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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/435,257	11/05/1999	PAUL A. CLEMONS	385A-US	4970

7590 01/16/2002

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EXAMINER
PARAS JR, PETER

ART UNIT	PAPER NUMBER
1632	20

DATE MAILED: 01/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/435,257	CLEMONS ET AL	
	Examiner	Art Unit	
	Peter Paras	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *19 and 40-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 20-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5*
4)☐ Interview Summary (PTO-413) Paper No(s) _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group II, claims 34-39 as well as generic claims 1-18 and 20-33, in Paper No. 7 is acknowledged. The traversal is on the ground(s) that the Examiner has not shown that a serious burden would be required to examine all the claims. In particular, Applicants submit that it would not have been undue to search the claims of Group I and Group II-IV. This is not found persuasive because it is maintained that each of the Inventions require a separate search status. In particular, Group I, directed to a fusion protein is not used in the methods of Group IV, which requires contacting a cell with a ligand. As such, the Invention of Group IV requires materially different reagents and technical considerations than methods employing the fusion proteins of Group I. Further, the fusion protein of Group I may be used in other methods than the methods of Groups II-IV. For example, fusion protein of Group I may be used as an antigen to produce antibodies in an animal. Therefore, it is maintained that these inventions are distinct due to their divergent subject matter (fusion protein, methods of producing genetically engineered host cells, method of multimerizing fusion proteins, etc.) and are thus, separately classified and searched. The requirement is still deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed

not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 19 and 40-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

Claim Objections

Claims 12-18, 22, 24-25, 27, 29, 31, 33, 35, 37 and 39 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must refer to claims in the alternative and cannot depend from another multiple dependent claim. Claim 12 does not refer to claims 5-11 in the alternative and claim 35 depends from another multiple dependent claim (claim 12). Claims 13-18, 22, 24-25, 27, 29, 31, and 33 depend from claim 12 and claims 37 and 39 depend from claim 35. See MPEP § 608.01(n). Accordingly, the claims 12-18, 22, 24-25, 27, 29, 30, 31, 33, 35, 37 and 39 have not been further treated on the merits.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 28 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 28 is directed to a host cell of human origin comprising a claimed nucleotide sequence. A broad interpretation of the claim encompassess a transgenic animal, the scope of which encompasses a human being. A human being is non-statutory subject matter. As such, the recitation of the limitation "non-human" would be remedial for claim 28. See 1077 O.G. 24, April 21, 1987.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26, 28, 30, 32, 34, and 38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are interpreted to read on a host cell *in vivo* the breadth of which encompasses a transgenic non-human animal when taken in light of the teachings of the specification.

While the specification has provided guidance for transformation of a cell *in vitro* with the claimed nucleotide sequences, the instant specification has failed to provide any relevant teachings, guidance, or working examples that teach how to create a transgenic non-human animal that expresses a nucleotide sequence encoding a CAB domain, wherein expression of a CAB domain fusion protein results in a particular phenotype. Moreover, the instant specification has failed to correlate expression of a CAB domain fusion protein with a specific phenotype in

a transgenic non-human animal while providing on prophetic discussions regarding the claimed transgenic animal.

As the specification fails to provide any relevant teachings or guidance with regard to the production of a transgenic animal as claimed, one of skill would not be able to rely on the state of the transgenic art for an attempt to produce CAB domain transgenic animals. This is because the state of the art of transgenics is not a predictable art with respect to transgene behavior and the resulting phenotype. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic animals comprising a transgene of interest; it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For instance, the level and specificity of expression of a transgene as well as the resulting phenotype of the transgenic animal are directly dependent on the specific transgene construct. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a resulting phenotype. This observation is supported by Wall (Theriogenology, 1996) who states that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine (Journal of Biotechnology,1994) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to

obtain good expression of a transgene (page 275, column 1, 1st paragraph): e.g., specific promoters, presence or absence of introns, etc. The claims as written do require a particular promoter to direct expression of a nucleotide sequence encoding a CAB domain. The instant specification has failed to describe any promoter that could be used to direct expression of said nucleotide sequence in a particular cell type to produce a desired phenotype. As such guidance is lacking in the instant specification, it fails to feature any correlation between the expression of a CAB domain transgene in any host animal, and, thus, a specific resulting phenotype.

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). This observation is specifically supported by Hammer et al. (Journal of Animal Science, 1986) who report the production of transgenic mice, sheep and pigs; however only transgenic mice exhibited an increase in growth due to the expression of the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. See also Ebert et al, (Molecular Endocrinology, 1988). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins et al. state that "a given construct may react very differently from one species to another." See page S39, Summary. Wall et al. report that "transgene expression and the physiological

consequences of transgene products in livestock are not always predicted in transgenic mouse studies." See page 62, first paragraph. Kappel et al. (Current Opinion in Biotechnology, 1992) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CpG methylation (page 549, column 2, 3rd full paragraph). Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, including pigs and rabbits, because, for example, the cis acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 238 239). Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of even one transgenic animal whose genome comprises a CAB domain transgene, it would have required undue experimentation to predict the results achieved in any one host animal comprising and expressing a CAB domain transgene, the levels of the transgene product, the consequences of that production, and therefore, the resulting phenotype.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the production of CAB transgenic animals, the lack of direction or guidance provided by the specification for the production of any transgenic animal expressing a transgene encoding a CAB domain for use, the absence of working examples for the demonstration or correlation to the production of a transgenic animal expressing a transgene

encoding a CAB domain, in particular when the transgene comprises CAB coding sequences under the control of any promoters, and more particularly when the expression of the transgene must occur at a level resulting in a corresponding phenotype, the unpredictable state of the art with respect to transgene behavior in transgenic animals of any species, and the breadth of the claim drawn to any animals it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claims 26, 28, 30, 34, 36, and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated host cell *in vitro* comprising a nucleotide sequence encoding a CAB domain, does not reasonably provide enablement for is not enabling for a host cell *in vivo* comprising a CAB domain protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.
The claims are interpreted to read on a somatic cell that has been transformed *in vivo* with one of the claimed nucleotide sequences.

While the instant specification has provided guidance for transforming an isolated somatic cell *in vitro*, the instant specification however, has not provided any relevant teachings, guidance, or working examples that teach or otherwise correlate to transformation of a cell *in vivo* with one of the claimed CAB nucleotide sequences. The specification has failed to provide any guidance or

working examples that correlate administration of said nucleotide sequence into a host with targeting of a particular cell type. Finally, the specification has failed to correlate expression of said CAB nucleotide sequence in a cell in vivo with any particular resulting effect. In light of the teachings of the instant specification is unclear what purpose expressing a CAB domain nucleotide sequence in the somatic cells of a host may serve other than to provide a therapeutic effect.

The art of *in vivo* somatic cell transformation falls into the realm of gene therapy. One of skill would not be able to rely on the state of the art of gene therapy to transform a somatic cell *in vivo* with a nucleotide sequence encoding a CAB domain protein. This is because the state of the art of gene therapy at the time the claimed invention was filed was unpredictable with respect to expression of a heterologous nucleotide sequence in a host cell *in vivo* and effect of the expression of said heterologous nucleotide sequence.

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by two reviews. Verma *et al.* teach that as of 1997, "there is still no single outcome that we can point to as a success story" (page 239, col. 1). The authors go on to state, "Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (page 239, col. 3). Anderson (1998) states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease" (page 25, col 1) and concludes, "Several major deficiencies still exist including poor delivery system, both viral and no-viral, and poor gene expression after genes

are delivered" (page 30). Besides the general expectation that it will require years of further research to develop effective gene therapy (Anderson, page 30), it would require extensive research to understand the fundamental biology of the system. Thus in view of the lack of guidance and direction provided by the specification for gene therapy of any disease, it would have required one of skill in the art undue experimentation to make and use the invention as claimed.

While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for in vivo gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The

teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for producing a somatic cell transformed *in vivo* with a claimed nucleotide sequence, the lack of direction or guidance provided by the instant specification for the production of a somatic cell transformed *in vivo* with a claimed nucleotide sequence, the absence of working examples the demonstrate or otherwise correlate to transformation of a somatic cell *in vivo*, and the unpredictability of the art of gene therapy with respect to transforming a somatic cell *in vivo*, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4, 20, 21, 23, 26, 28, 30, 32, 35, 36, and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 3 are indefinite as written. The claims are directed to recombinant nucleic acid sequences that encode portions of calcineurin A and calcineurin B, wherein the portions are comprised of sequences of calcineurin A and calcineurin B. For example claim 2 recites that the claimed nucleotide sequence can encode amino acid residues 12-394, 12-370, or 340-394 of calcineurin A. The claims are indefinite because there is no uniform numbering system of amino acid residues known in the art and because the specification has not provided a sequence (either amino acid or nucleotide) of either calcineurin A or calcineurin B that would guide the skilled artisan with regard to the numbering of the claimed sequences. Neither the claims nor the specification have defined the cal A or cal B sequences from which the claimed "portions" are obtained. As such the skilled artisan does not know which calcineurin A or calcineurin B sequences correspond to the claimed portions of cal A or cal B rendering the claims indefinite. Claims 4, 20, 21, 23, 26, 28, 30, 32, 35, 36, and 38 depend from claims 2 and 3. Clarification is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4,11, 20-21, 26, 28, 34 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Guerini et al (PNAS, 1989, 86: 9183-9187).

For the purposes of the rejections under 102, the claims are interpreted to read on a nucleotide sequence encoding a portion of calcineurin A and a portion of calcineurin B, wherein a portion is interpreted to mean any amino acid (s) from either calcineurin A and calcineurin B.

Guerini et al teach a nucleotide sequence that encodes portions of the calcineurin A and calcineurin B. In particular, Guerini teaches a nucleotide sequence that encodes amino acid residues 12-394, 12-370, 340-394 of human calcineurin A (100% similarity, see PTO sequence search-which searched a nucleotide sequence encoding a fusion of a.a. residues 12-394 of cal A and 3-170 of cal B against the sequence databases, attached to the instant office action) and a portion of calcineurin B sequence. Guerini et al have taught cloning of said sequence into a vector that was transformed into a host cell *ex vivo*. See Materials and Methods section on pages 9183-9184. As the sequence of Guerini was obtained from a human brainstem and basal ganglia cDNA library, it is inherent that Guerini has taught a human cell comprising the claimed

sequence as the claimed nucleotide sequence was originally contained in a human cell. Thus, the teachings of Guerini anticipate all of the instant claim limitations.

Claims 1 and 3-4, 11, 20-21, 26, 28, 34 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Guerini et al (DNA, 1989, 8(9): 675-682).

Guerini et al teach a nucleotide sequence encoding residues 3-170 of calcineurin B and a portion of calcineurin A (see attached results of the PTO sequence search, same parameters as above). Guerini et al have taught cloning of said sequence into a vector that was transformed into a host cell *ex vivo*. See Materials and Methods section on pages 9183-9184. As the sequence of Guerini was obtained from a human brainstem and basal ganglia cDNA library, it is inherent that Guerini has taught a human cell comprising the claimed sequence as the claimed nucleotide sequence was originally contained in a human cell. Thus, the teachings of Guerini anticipate all of the instant claim limitations.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5-11, 20, 23, 26, 28, 34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guerini et al (PNAS) or Guerini (DNA) taken with Chaudhuri et al (Biochemical and Biophysical Research Communications, 1995, 215(2): 781-790) and Crabtree (U.S. 6,164,787).

For the purposes of the rejections under 103, the claims are interpreted to read on a nucleotide sequence encoding a portion of calcineurin A and a portion of calcineurin B, wherein a portion is interpreted to mean any amino acid (s) from either calcineurin A and calcineurin B.

Guerini (PNAS) et al teach a nucleotide sequence encoding a portion of calcineurin A and a portion of calcineurin B. Guerini (DNA) et al teach a portion of a nucleotide sequence encoding a portion of calcineurin A and a portion of calcineurin B.

Guerini et al (PNAS) and Guerini et al (DNA) have not taught a nucleotide sequence encoding calcineurin A and calcineurin B that further comprises a heterologous domain.

However at the time the claimed invention was filed, it was routine in the art and well within the purview of the ordinary artisan to create a nucleotide sequence that encode fusion proteins comprising a domain of a protein of interest and a heterologous domain for use in the two hybrid system to perform binding assays with other proteins. In particular, Chaudhuri et al have taught that a nucleotide sequence encoding a portion of calcineurin A and a portion of calcineurin B in can be used in a two hybrid assay to study binding of other peptides (see abstract and materials and methods and throughout). Crabtree et

al have taught the use of Gal4, VP16, cell surface receptor intracellular domains, and ssn-6/TUP-1 domains in the two hybrid system to assay binding partners of any protein of interest, including calcineurin (see columns 13-14, 17, and 27-28). Crabtree et al have also taught that such a nucleotide sequence may be inserted into a viral for vector for the purpose of transforming a host cell, particularly a human cell *in vitro* or *ex vivo*, see columns 32-33, as well as the working examples.

Accordingly, in view of the ordinary state of the art as presented by Chaudhuri et al and Crabtree et al it would have been obvious to modify the sequences of Guerini et al (PNAS) or Guerini et al (DNA) to create nucleotide sequences that encode fusion proteins comprising a portion of calcineurin A, calcineurin B, and a heterologous domain for use in the two hybrid system to assay for binding partners. It would have been obvious to insert the sequence of Guerini (PNAS) or Guerini (DNA) into a viral vector in order to transform eukaryotic cells as taught by Crabtree. One of ordinary skill would have been sufficiently motivated to make such modifications, as it was an art recognized goal to assay for binding partners as taught by Chaudhuri and Crabtree.

Thus, the claimed invention, as a whole, was clearly prima facie obvious in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340 The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Peter Paras, Jr.

Art Unit 1632

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